REMARKS

Claim 9 is pending, and is amended into independent format. Claims 1-8 and 10-19 are cancelled without prejudice to the prosecution of their subject matter in other applications. An abstract on a separate page has been added, as required by the Examiner. The title is amended to more particularly reflect the claimed subject matter.

Applicants note that the instant application, as originally filed on September 21, 2001 as a national stage filing of PCT International Application No. PCT/US00/06862 filed March 15, 2000, contains Claims 1-19 and not 1-20 as stated in the pending Official Action. Therefore, there has not been a claim 20 in this application.

Claims 9,10 and 18 are rejected under 35 U.S.C. 101 and 35 U.S.C. §112. For reasons detailed below, the rejections should be withdrawn and the claims should be allowed to issue.

1. **The Invention**

The present invention relates to a transgenic animal containing a transgene comprising a gene encoding a reverse tetracycline controlled transactivator, operably linked to the EF1-α promoter. This transgene may be used as one component of a two component system, wherein a second transgene comprises a gene of interest, such as an oncogene, operably linked to a second promoter and a tet-operator sequence. In the presence of tetracycline, the gene of interest is expressed. Such two component systems previously known in the art featured a reverse tetracycline controlled transactivator under the transcriptional control of promoters other than the EF-1α promoter, and the

incorporation of the EF-1α promoter, according to the present invention, confers substantial and unexpected advantages.

2. **An Abstract In Proper Form Is Provided**

The abstract filed in instant application is improper because it is the front page of WO 00/55310 of which instant application is a national stage filing.

Applicants have herein amended the specification to insert a new page containing an abstract comprising of a single paragraph on a separate sheet within the range of 50 to 150 words. Applicants further note that no new matter has been added by the amended abstract.

3. **Claim 9 Is Of Proper Form**

Claims 9 and 10 are objected to because of dependence on claim 1 which is in a non-elected group.

Claim 9 as amended is an independent claim, and claim 10 is canceled, so that the objection should be removed.

4. **Claim 9 Is Supported By A Well Established Utility**

Claims 9 and 10 are rejected under 35 U.S.C. §101 for lacking a specific and substantial asserted utility or a well-established utility because, according to the Examiner:

> "A substantial utility is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. .....Uses of the

> claimed transgenic non-human animal as an animal model to study effects of specific genes in animals, or to screen for anti-tumoral or other pharmacological effects of drugs or small molecules, are not considered substantial utilities....."

The Examiner alleges that the specification fails to identify what disease or disorder is associated with the claimed transgenic non-human animals so that there is no correlation between a phenotype of the claimed animal and a particular disease or disorder, and contends that Claims 9 and 10 lack a specific utility.

Claim 9 is drawn to a transgenic mouse wherein the transgene is a reverse tetracycline controlled activator the expression of which is controlled by the human Translation Elongation Factor-1α promoter. The invention specified by claim 9 has a substantial and well-established utility for reasons set forth below.

The Examiner alleges that:

> "the specification fails to identify what disease or disorder is associated with the claimed transgenic non-human animals and that there is no correlation between a phenotype of the claimed animal and a particular diseases or disorder"

The Examiner has failed to consider the proper well-established utility of the transgenic animal of the instant invention. The utility of the instant invention is an improved and consistent expression of the reverse tetracycline controlled activator in tissues of a transgenic animal resulting from the promoter activity of the EF-1α promoter. The transgenic animal of the instant application does not require that any disease or other overt disorder phenotype be associated with it. In fact, such phenotype would be regarded as an undesirable property, which would diminish the animals' usefulness as a model system. Thus the instant application states at page 11, lines 22-31 that:

> "The present invention provides a vector which is directed to providing a consistent cellular expression of the tetracycline repressor in cells. Such a vector may be

> useful in situations requiring inducible gene expression in a tissue specific or generalized manner in animal of plant models. In one embodiment of the invention, pharmacological products are monitored to determine use in medical applications. In the preferred embodiment monitoring is of the gene changes associated with cellular process such as aging, cancer, development, differentiation and growth".

Applicants invite the Examiners attention to the following United States Patents and journal articles that document the development and utility of tetracycline regulated transgenic animals of which the instant invention presents an improvement. These citations are attached to this response as Exhibits (1)- (7), respectively.

(1) United States Patent No. 5,922,927 by Bujard et al., "Methods For Producing Tetracycline-Regulated Transgenic Mice, issued July 13, 1999;

(2) United States Patent No. 5,917,122 by Byrne, "Tetracycline Repressor-Mediated Binary Regulation System For Control Of Gene Expression In Transgenic Mice," issued June 29, 1999 ("the '122 patent");

(3) United States Patent No. 5,912,411 by Bujard et al., "Mice Transgenic For A Tetracylcine-Inducible Transcriptional Activator," issued June 15, 1999 ("the '411 patent");

(4) Chin et al. 1999, "Essential role for Ras in tumour maintenance" Nature 400(6743) 468-472;

(5) Chin et al. (2000) "Flipping the oncogene switch: illumination of tumour maintenance and regression" Trends Genet 16(4): 147-150;

(6) Wang et al. 2004 "Inducible silencing of KILLER/DR5 in vivo promotes bioluminescent colon tumor xenograft growth and confers resistance to chemotherapeutic agent 5-fluorouracil" Cancer Res 64(18):6666-6672; and

(7) Vitale-Cross et al. (2004) "Conditional expression of K-ras in an epithelial compartment that includes the stem cells is sufficient to promote squamous cell carcinogenesis" Cancer Res 15(64):8804-8807.

The references cited as items (1)-(7) are listed on a PTO-1449 form attached hereto as citations A-G, where citing said references is not an admission that they constitute prior art.

The utility of the transgenic animals of instant invention will be easily recognizable to those of ordinary skill in the art as evidenced by the preceding citations. The specification of the instant invention clearly establishes that the invention specified by Claims 9 and 10 have a substantial and well-established utility.

The "New Therapeutic Patent Utility Guidelines" (Federal Register, July 14, 1995, pages 36263-36365, paragraph B2(a)) states that:

> If the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., a specific utility) and that assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. Credibility is to be assessed from the perspective of one of ordinary skill in the art in view of any evidence of records (e.g., data, statements, opinions, references, etc.) that is relevant to the applicant's assertions. An applicant must provide only one credible assertion of specific utility for any claimed invention to satisfy the utility requirement.

For the reasons set forth above, and because claim 10 is cancelled, Applicants respectfully request that the rejection be withdrawn.

5. **Claim 9 Is Definite**

Claims 9 and 10 are rejected as indefinite under 35 U.S.C. §112, second paragraph, as indefinite.

The Examiner contends that the phrase " a tetracycline inducible operator binding element under control of the nucleic acid encoding the transactivator (claim 1 line 7-9) is indefinite because "it is unclear how a coding sequence could control a tetracycline inducible operator binding element.: The Examiner contends that the phrase " gene of interest under control of the promoter" (line 10 of claim 1, upon which claim 9 depends) is indefinite because it is unclear whether the promoter is the E1-α promoter.

Both phrases are absent in the amended claim 9, and claim 10 is canceled, so that this rejection should be withdrawn.

6. **Claim 9 Is Adequately Described By The Specification**

The Examiner has rejected Claims 9, 10 and 18 under U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner contends that the claimed subject matter was not described in a way which would convey, to the skilled artisan, that Applicants were in possession of the invention, because claim 9 encompasses many different species of transgenic animal, the phenotypes of which would not be predictable.

Applicants respectfully disagree, because the person of skill in the art, at the earliest priority date claimed by the instant application, March 15, 1999, would have been able to produce a wide variety of transgenic animals and use them in drug screening assays, so that Applicants were in possession of the claimed invention . Nonetheless, to

put this application in order for allowance, Applicants have amended claim 9 to be limited to mice, and have canceled claims 10 and 18 without prejudice. Accordingly, the rejection should be withdrawn.

7. **Claim 9 Is Enabled By The Specification**

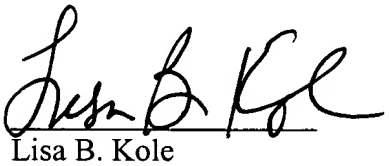
The Examiner has rejected Claims 9, 10 and 18 under U.S.C. §112, first paragraph, as not enabled. The Examiner contends that because claim 9 encompasses many different species of transgenic animal of unpredictabnle phenotypes, whereas the specification describes the preparation of a transgenic mouse, the claim is not enabled.

Applicants respectfully disagree, because the person of skill in the art, at the earliest priority date claimed by the instant application, March 15, 1999, would be able to produce a wide variety of transgenic animals without undue experimentation. Nonetheless, to put this application in order for allowance, Applicants have amended claim 9 to be limited to mice, and have canceled claims 10 and 18 without prejudice. Accordingly, the rejection should be withdrawn.

8. Conclusion

For all the foregoing reasons, it is requested that the rejections be withdrawn and that claim 9 be allowed to issue.

Respectfully submitted,



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